

### **REMARKS**

Upon entry of this Amendment, claims 34-44, 47 and 50-51 will be pending. Claims 34-49 were pending in the subject application. Claims 34-35, 38-39, 44 and 47 have been amended. Claims 45-46 and 48-49 have been cancelled. Claims 50-51 have been added. Applicants have amended the claims without prejudice to their right to pursue any cancelled or deleted subject matter in one or more future patent applications.

Support for amended claims 34 and 47 may be found in the specification, *e.g.*, at Example 6 and original claim 46. Support for amended claim 35 may be found in the specification, *e.g.*, at page 7, lines 19-25. Amended claims 38-39 may find support in the specification, *e.g.*, at original claim 38. Support for amended claim 44 may be found in the specification, *e.g.*, at original claim 44. Amended claim 47 may find support in the specification, *e.g.*, at page 5, lines 8-9. New claims 50-51 may find support in the specification, *e.g.*, at page 2, lines 27-29, page 5 lines 20-22, and page 6, lines 16-18.

The amendments raise no issue of new matter.

#### **A. Claim 35 is definite**

The United States Patent and Trademark Office ("the Office") rejected claim 35 under 35 USC §112(2) for allegedly being indefinite because the scope of the phrase, "substantially pure" is apparently unknown. Applicants traverse the rejection.

Amended claim 35 now recites in relevant part – "stereochemically pure." Applicants submit that the phrase, "stereochemically pure" particularly points out and distinctly claims the invention Applicants deem as theirs because the scope of the phrase is clearly discernible from the specification. For example, at page 7, lines 19-25, the specification provides that "stereochemically pure" refers to an enantiomeric excess from at least 70% to at least 98%, and where, *e.g.*, at least 80% enantiomeric excess means that the ratio of I to its enantiomer is 90:10 in the mixture in question. Consequently, claim 35 is not indefinite.

Applicants, therefore, respectfully request that the §112(2) rejection be reversed.

#### **B. Claim 36 is enabled**

The Office rejected claim 36 under 35 USC §112(1) for allegedly not being enabling for "any and all salts" with respect to the claimed pharmaceutical composition. Applicants traverse the rejection.

For example, amended claim 34, from which claim 36 depends, now recites in relevant part – "pharmaceutically-acceptable salt". The Office acknowledged that the specification is enabled for

compositions comprising the compound of formula (I) and pharmaceutically acceptable salts thereof. See pages 2-3 of the Office Action. Consequently, because claim 36 depends from amended claim 34, which is enabled as acknowledged by the Office, claim 36 is enabled.

Also, Applicants have cancelled claims 46 and 48 per the Office's request for such amendments in view of an amended claim 34.

Applicants, therefore, respectfully request that the §112(1) rejection be reversed.

**C. Claims 38-45 and 48-49 are enabled**

The Office rejected claims 38-45 and 48-49 under 35 USC §112(1) for allegedly not being enabling for certain diseases and disorders. See page 3 of the Office Action. Applicants respectfully traverse the rejection.

Without conceding to the correctness of the Office's position and merely to advance prosecution, Applicants have amended claims 38, 39, and 44 and cancelled claims 45, 48 and 49. Applicants submit that amended claims 38, 39, and 44, and claims 40-43, are enabled. For example, amended claim 38 now recites in relevant part:

wherein the disease or disorder is selected from the group consisting of schizophrenia, an anxiety disorder, depression, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder and mania in bipolar disorder.

In fact, the Office acknowledged that the specification is enabled for these disorders. See page 3 of the Office Action. And, amended claim 46 is enabled as previously discussed herein. Consequently, claims 38-44 and 48 are enabled.

Applicants, therefore, respectfully request that the §112(1) rejection be reversed.

**D. Claims are novel**

The Office rejected claims 34, 35 and 46 under 35 USC §102(b) for allegedly being anticipated by Bøgesø et al., *J. Med. Chem.* 1995, 38:4380-92 ("the Bøgesø reference"). Applicants traverse the rejection and respectfully request it be reversed.

For a claimed invention to be anticipated, a single reference must teach each and every aspect of the claimed invention. The Office alleges that the Bøgesø reference describes the trans form of the compound of the instant invention.

However, for example, amended claim 34 recites in relevant part:

[a] compound having a name of *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine...

The Bøgesø reference fails to teach the (1R,3S)-enantiomer of amended claim 34. Consequently, the Bøgesø reference does not teach each and every aspect of claim 34. Also, because of its dependency from claim 34, amended claim 35 is not anticipated. Because claim 46 has been cancelled, the rejection is moot with respect to it. Claims 34 and 35, therefore, are novel.

Accordingly, Applicants request the §102(b) rejection be reversed.

#### **E. Claims are not obvious**

The Office rejected claims 34-49 under 35 USC §103(a) for allegedly being obvious over the by the Bøgesø reference and EP 0 638 073 ("EP'073") ("the combined references"). Applicants traverse the rejection and respectfully request it be reversed.

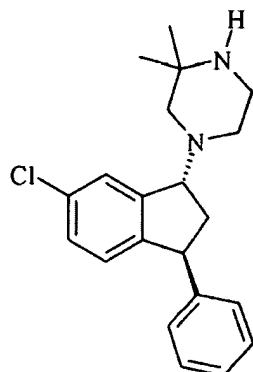
For a claimed invention to be obvious, the teaching of a prior art reference or teachings of a combination of prior art references must be viewed in light of four factual inquiries:

- (a) determining the scope and contents of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating evidence of secondary consideration.

See *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459,467 (1966). Whether the reference(s) teach, suggest or motivate one of ordinary skill in the art to combine the reference(s) in a manner that achieves the claimed invention can be helpful in this determination for obviousness. See *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007); see also, e.g., *Cordis Corp. v. Medtronic AVE Inc.* 511 F.3d 1157 (Fed. Cir. 2008).

In this instance, the Bøgesø reference fails to make the present invention obvious. For example, amended claim 34 recites:

[a] compound having a name of *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine and a formula of:



(I);

or a pharmaceutically acceptable salt thereof. (Hereinafter, "Compound I").

In contrast, the Bøgesø reference arguably teaches a racemic mixture of the compound of formula (I), compound 38. If the Bøgesø reference teaches the racemate, it does so generically because the schematic of Figure 1 teaches that moiety B can be the piperazine group associated with Compounds 28-31 and 37-55, when  $R_3$  is H and  $R_1$  and  $R_2$  are as defined in Tables 3-5. See p. 4382. Arguably the Bøgesø reference does not even teach the racemate generically because the piperazine group is clearly associated with Compounds 28-31 and 37-55, where when  $R_3$  is H and  $R_1$  is 6-Cl, then  $R_2$  is not phenyl. See e.g., Tables 4 and 5. Even if the Bøgesø reference teaches the racemate generically, as the Office deems it does (see Office Action, p. 6-7), the Bøgesø reference unmistakably fails to teach the specific enantiomer of amended claim 34.

In addition to being silent as to specifically Compound I, the Bøgesø reference fails to provide an apparent reason to modify its compounds to achieve Compound I. For example, its compounds (-)38, (+)38, 38, (-)41, (+)41 and 41, appear to be the closest structurally related compounds of the Bøgesø reference to Compound I of amended claim 34. The Bøgesø reference teaches that the (-)38 and (-)41 enantiomers are potent 5-HT<sub>2</sub> antagonists and potent D<sub>1</sub>/D<sub>2</sub> antagonists with a high affinity for  $\alpha_1$  andrenoceptors and no inducement of catalepsy, and the (+) enantiomer is a potent inhibitor of DA and NE uptake. See e.g., page 4386, text and Table 5. The Bøgesø reference further teaches that the racemic compound 38 and (-)38 enantiomer "have unusually potent effects" compared to the 4'-fluoro substituted derivative (compound 10), when it had been reported previously that such fluoro atom was necessary for a potent effect to be achieved. See e.g., page 4385, text; see also, e.g., Tables 3 and 5. In fact, the Bøgesø reference teaches that the (-)38 and (-)41 enantiomers and two other derivatives, "fulfill the goal of being a mixed antagonist" with potential as an atypical antipsychotic, and thus, would be selected for preclinical studies. See e.g., page 4386, text.

Indeed, by its teaching that compounds 38 and 41 and their respective enantiomers have, *e.g.*, desirable potencies/affinities and the like with respect to antipsychotic drugs, the Bøgesø reference teaches away from the present invention. The Bøgesø reference teaches away because, in its acknowledging these desirable qualities of compounds 38 and 41 and their respective enantiomers, not to mention at least the two other derivatives, the Bøgesø reference fails to provide an apparent reason for one of ordinary skill in the art to modify its teaching of the trimethylpiperazine derivatives of 38 and the 4'-fluoro substituted derivatives of 41 so as to achieve the specific enantiomer of amended claim 34.

The Bøgesø reference also teaches away because a particular goal of the Bøgesø reference "was to obtain new compounds with mixed profiles (D<sub>1</sub>, D<sub>2</sub>, 5-HT<sub>2</sub> and  $\alpha_1$ ) together with potent D1 activity." *See e.g.*, page 4381. This goal was achieved, and in fact, acknowledged with respect to compounds 38 and 41 and their respective enantiomers, with continuing study of, *e.g.*, compounds 38 and 41 and their enantiomers, as previously mentioned. *See also, e.g.*, page 4386, text. Additionally, the Bøgesø reference is silent with respect to any non-4'-fluoro substituted dimethylpiperazine derivatives, much less with respect to Compound I of amended claim 34. The Bøgesø reference, therefore, teaches away from the present invention's *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I).

Consequently, the Bøgesø reference fails to teach, much less suggest or motivate, one of ordinary skill in the art to modify its teachings, *e.g.*, of compounds 38 and 41 and their respective enantiomers so as to achieve the *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I) of the present invention.

Furthermore, EP'073 cannot correct the deficiencies of the Bøgesø reference. Although EP'073 generically teaches the racemate of Compound I of the present invention (*see e.g.*, paragraph [0002]), EP'073 is silent on a specific teaching of the enantiomer of the present invention. EP'073 also discloses generically compounds ( $\pm$ )38 and ( $\pm$ )41 of the Bøgesø reference (*see e.g.*, paragraph [0002]), as well as a maleate salt of compound ( $\pm$ )38 (*see* "Compd. 10", page 9, lines 6-7) and the hemifumarate salt of compound ( $\pm$ )41 (*see e.g.*, Example 2). Yet, the Bøgesø reference teaches with respect to 6-Cl dimethylpiperazine derivatives of formula (I), a preference for 4'-fluoro substituted dimethylpiperazine derivatives, and not the non-4'-fluoro substituted dimethylpiperazine derivative that is the enantiomer of amended claim 34. *See e.g.*, Examples 2, 4, and 5, and Compds. 18, ( $\pm$ )40, (-)40 and (+)40. Similarly, with respect to 6-Cl trimethylpiperazine derivatives of formula (I), the Bøgesø reference teaches a preference for 4'-fluoro substituted dimethylpiperazine derivatives; and again, not the non-4'-fluoro substituted dimethylpiperazine derivative that is the enantiomer of amended claim 34. *See e.g.*, Examples 3 and 6, and Compds. 9-12 and 38.

In fact, by focusing its teachings of a 4'-fluoro substituted di- and tri-methylpiperazine derivatives of formula (I), EP'073 teaches away from the present invention because as a result it fails to provide one of ordinary skill in the art an apparent reason to combine the known elements of the Bøgesø reference with the known elements of EP'073 to achieve the Compound I of the present invention. As discussed previously, the known elements of the Bøgesø reference are a generic teaching of the racemate of Compound I without more, and 6-Cl trimethylpiperazine derivatives (*i.e.*, (-)38, (+)38, (±)38), and 4'-fluoro substituted dimethylpiperazine derivatives (*i.e.*, (-)41, (+)41 and (±)41), which have potent effects so as to have met the goal of being mixed antagonists, while the known elements of EP'073 are also a generic teaching of the racemate of Compound I without more, and a preference for 6-Cl-4'-fluoro substituted di- and tri-methylpiperazine derivatives. Clearly, EP'073 fails to provide any apparent reason to combine its known elements with those of the Bøgesø reference so as to achieve the specific enantiomer of amended claim 34. Additionally, because of these teachings, EP'073 fails to suggest or motivate one of ordinary skill in the art to modify the known elements of the Bøgesø reference so as to achieve the specific enantiomer of amended claim 34. Consequently, the present invention is unobvious over the Bøgesø reference in view of EP'073.

Additionally, only with hindsight and use of Applicant's own specification as a blueprint, would one of ordinary skill in the art be motivated to modify the Bøgesø reference and/or EP'073 to achieve specifically the *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I) of the present invention. However, this is improper since using hindsight in finding the claimed invention obvious over prior art is impermissible. *See e.g.*, MPEP §2142 (providing that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art"); *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), at 22 (stating expressly that hindsight analysis of a patent challenged for obviousness is still to be avoided).

Yet the Office's conclusion that because the Bøgesø reference discloses structurally similar compounds and generically discloses the racemate of the claimed compound (*see supra*), it would have been obvious in view of EP'073 for one skilled in the art to modify compound 38 of the Bøgesø reference so as to achieve the specific enantiomer of amended claim 34 improperly uses hindsight. As discussed previously, the combined references each lack any apparent reason from which one skilled in the art would be motivated to achieve the present invention's compound. Rather, the Office merely uses Applicants' invention as a "road map" to piece together the teachings of the prior art in order to render the claimed invention obvious.

Thus, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I) of amended claim 47 is not obvious in view of the combined references.

Furthermore, a determination of obviousness of a compound rests on more than its structure. "From the standpoint of patent law, a compound and all of its properties are inseparable." *In re Papesch* (315 F.2d 381, 391 (C.C.P.A. 1963). Evidence of a difference between the claimed compound and the prior art may take the form of "a comparison of test data showing that the claimed compositions possess unexpectedly improved properties...that the prior art does not have, that the prior art is so deficient that there is no motivation to make what might otherwise appear to be obvious changes, or any other argument or presentation of evidence that is pertinent." See e.g., *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990)(*en banc* endorsement of *In re Papesch*); *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997)(citing *In re Dillon*). Further, whether a difference is "striking" depends, not alone on the numerical ratio of the quantified value of the property being compared, but on the significance of that difference", such as whether the difference is of "any practical advantage". *In re D'Ancicco*, 439 F.2d 1244, 1248 (C.C.P.A. 1971).

Accordingly, even though Compound (I) of amended claim 34 is structurally similar to the prior art compounds and is directed to comparable uses based on similar activity profiles as that of the combined references, the compound has surprising and unexpected properties compared to the prior art compounds, and therefore is not obvious.

For example, Applicants have surprisingly and unexpectedly found that Compound I is a weak inhibitor of Cytochrome P450 2D6, an enzyme associated with drug metabolism. Besides being surprising and unexpected, this finding also was unpredictable in view of Cytochrome P450 2D6 inhibitory activity data for the prior art compounds. In support of evidencing the difference between Compound I and the prior art compounds, Applicants submit the declaration of co-inventor Benny Bang-Andersen under 37 C.F.R. 1.132.

Further, Compound I of amended claim 34 unmistakably is not obvious because it would be clear to one skilled in the pharmaceutical arts that the 'striking' difference in the Cytochrome P450 2D6 inhibitor activity of Compound I compared to the prior art compounds has at least desirable one practical advantage. For example, because of its being a weak inhibitor of Cytochrome P450 2D6 activity, Compound I likely has a reduced potential for drug-drug interaction when given in combination with another drug(s). A reduced potential for drug-drug interaction is advantageous as it reduces the likelihood of adverse effects with a patient on a combination drug therapy regime. This often is the case with, e.g., a schizophrenic patient.

Therefore, because Compound I of amended claim 34 has a surprising and unexpected property, which is unpredictable and advantageous in a practical sense, the claimed Compound I is not obvious in view of the combined references.

Besides, Compound I of amended claim 34 is different from the prior art compounds, and thus not obvious, because as discussed previously, it is very evident that the combined references are quite deficient such that there is no motivation therein to make what may appear to be an obvious change. See *In re Dillon, supra*.

Accordingly, claims 35-44 and 47 are patentably distinguishable over the combined references because of their dependency from amended claim 47. Claims 45, 48 and 49 have been canceled, therefore, the obviousness rejection with respect to these claims is moot.

For the foregoing reasons, claims 35-44 and 47 are not obvious in view of the combined references. Applicants respectfully request the § 103(a) rejection be withdrawn.

#### **F. Provisional nonstatutory double patenting**

The Office has provisionally rejected claims 34-49 on the ground of nonstatutory obvious-type double patenting as being unpatentable over claims of copending USSN 11/816,394 ("the '394 application"), and over claims of copending USSN 11/814,403 ("the '403 application") in view of EP'073.

Applicants submit that they will consider filing a terminal disclaimer(s) upon indication of allowable claims if the rejection(s) are maintained at that time.

#### **G. Potential §103(a)/ §102(e), (f) or (g) rejection**

The Office states that the '394 application and the '403 application would be basis for a rejection under 35 USC §103(a) if these commonly assigned applications qualify as prior art under 35 USC §102(e), (f) or (g). In order to preclude the rejection, Applicants submit under 35 USC §103(c) and 37 CFR 1.78(c) that the '394 application and the '403 application were owned by or subject to an obligation of assignment to the same entity at the time the present invention was made.

#### **H. IDS reference**

The Office noted that a copy of the disclosed Cox reference "is not seen in the file" and "[a] copy is needed for consideration." See page 8 of the Office Action. Because of an inadvertent error of Applicants with respect to the 2/21/08 SIDS that disclosed the Cox reference, Applicants respectfully request that the Office confirm whether or not it deems a copy of Cox is needed for consideration.

Applicants make this request since they now have found that the citation for the Cox reference on the SB08 Form of 2/21/08 inadvertently included the phrase, "P.6 of 512", which refers to the page of the specification of related USSN 11/816,383 wherein the Cox reference is disclosed. The full Cox reference, therefore, was being disclosed, not only page 6, as it may have appeared. Also, Applicants statement in connection with the 2/21/08 SIDS provided that a copy of the Cox reference was not being provided

because of its voluminous nature. The Cox reference ("Preparative Enantioselective Chromatography", Oxford, UK: Blackwell Publishing LTD. 2005) is a 344 page book. However, as also stated on 2/21/08, Applicants will make all reasonable efforts to provide a copy of the book if the Office deems a copy is needed.

Applicants thank the Office for confirmation whether it deems a copy of Cox is needed for consideration in view of the foregoing.

#### **I. Conclusion**

Applicants believe the claims are in condition for allowance, and earnestly solicit an early Notice of Allowance. Applicants invite the Examiner to contact the undersigned below if deemed helpful in advancing prosecution of the instant application.

Also, authorization is given to charge the Petition for Extension of Time and any additional fee, as well as credit any overpayment, to Deposit Account Number 50-3201.

Respectfully submitted,

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